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Web-based tailored psycho-education for breast cancer patients at the onset of the survivorship phase: a multicenter randomized controlled trial.

Running title: Breast cancer web-based psycho-education

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ABSTRACT

Context: Many breast cancer patients have unmet informational and psychosocial needs after treatment completion. A psycho-educational intervention may be well-suited to support these patients.

Objectives: The purpose of this multicenter randomized controlled trial was to examine the effectiveness of a web-based tailored psycho-educational program (ENCOURAGE) for breast cancer patients which aims to empower patients to take control over prevailing problems.

Methods: Female breast cancer patients from two hospitals in the Netherlands who recently completed (neo-)adjuvant chemotherapy were randomly assigned to standard care or 12-week access to the ENCOURAGE program providing fully automated information, problem-solving strategies, resources and services for reported problems. At 6 and 12 weeks, patients completed self-report questions on optimism and control over the future (primary outcome), feelings of being informed and acceptance of the illness. At baseline and 12 weeks, distress and quality of life questionnaires were completed.

Results: 138 patients were included. Almost **all patients (67/69)** visited ENCOURAGE as requested. No differences between the control and the intervention group were observed for primary and secondary outcomes. An unplanned subgroup analysis showed that in clinically distressed patients (N=57 at baseline; 41%), use of the ENCOURAGE program increased optimism and control over the future at 12 weeks more than in patients in the control group (Cohen's *d*=0.65).

Conclusions: Although the effectiveness was not demonstrated, a subgroup of women treated for breast cancer can probably be supported by the program. The results of the current study are a starting point for further development and use of the program.

Keywords: Web, breast cancer, psycho-education, self-care.

INTRODUCTION

The presence of psychosocial and physical symptoms after completion of breast cancer treatment is well-known [1-3]. Patients struggle with psychological issues as well as physical symptoms [4,5]. Many patients wish for information about symptoms/problems that may arise after treatment completion and about strategies how to cope with these problems [1,6]. However, interventions that focus on supporting breast cancer patients during the first year after **primary** treatment completion (i.e. re-entry phase) are scarce [7-9]. Psycho-education, which combines patient education with activities such as advice on self-management strategies and/or counseling [10,11], may be well-suited to support patients during the re-entry phase. The few psycho-educational interventions that focused on breast cancer patients in the re-entry phase - delivered in multi-sessions via group, face-to-face and/or video format - showed positive effects on outcomes such as anxiety, depression, fatigue and quality of life [12-14]. Benefits were also found for a brief 2-hour psycho-educational group session regarding knowledge and preparedness for the re-entry phase [8]. These interventions required involvement of (a) health care professional(s) and, therefore, were relatively labor intensive. Considering the growing number of breast cancer survivors, the internet has been viewed as a cost-effective medium to support patients [15]. New web-based programs emerge at a rapid pace [16], but **only few** web-based interventions for breast cancer patients in the re-entry phase are available at present.

Therefore, we developed the ENCOURAGE program. This is a web-based tailored psycho-educational program for breast cancer patients in the re-entry phase which aims to empower patients to take control over prevailing problems and to adjust to life after treatment. We adopted a problem-solving orientation in the development of ENCOURAGE. This orientation involves appraising problems as challenges, be optimistic about the solvability of problems and having a sense of personal control over the problems [17]. According to the

theory of problem solving, when patients learn to identify and solve problems, their sense of control and confidence will increase and these changes will in turn enhance adjustment [18,19]. Additionally, research showed that the use of active approach-oriented coping strategies (e.g. emotional expression, seeking social support) is related to perceived control and enhances healthy adjustment to cancer [20-24]. The possible solutions to a problem offered by ENCOURAGE emphasize the use of approach-oriented coping strategies.

A randomized prospective study was performed to measure the effects of the ENCOURAGE program. We hypothesized that breast cancer patients who use the program report a larger increase in optimism and feelings of control over the future than patients who receive standard care. Patients' feelings of being informed, acceptance of the illness, distress and quality of life were also studied.

METHODS

Patients

Patients were recruited at the outpatient clinics of Medical Oncology Departments **between January 2013 and October 2014** in two hospitals in the North-Eastern part of the Netherlands: the Martini Hospital (MH, Groningen) and the University Medical Center Groningen (UMCG, Groningen). The study was approved by the medical ethical committee and was registered (ClinicalTrials.gov, Identifier NCT01834521). Informed consent was obtained from all included patients. **Female breast cancer patients diagnosed with primary breast cancer who completed curative-intent primary treatment within the past 6 months (defined as surgery combined with any type of (neo)adjuvant chemotherapy) were eligible. Patients might still be receiving immunotherapy, hormonal therapy and/or radiotherapy**.

Other inclusion criteria were: ≥18 years of age, ability to comprehend Dutch reading and writing, having access to the internet including an e-mail address (at home or via family/friends) and physically and cognitively able to participate. Patients were not eligible when they were diagnosed with recurrent and/or metastasized breast cancer.

Procedures

This was a prospective, randomized controlled, multi-center, parallel-group study. Patients who were identified as eligible received a study information letter, an informed consent form, the baseline questionnaire (T0), an address form, two general information leaflets ('Breast cancer' and 'Continuing life after cancer' of the Dutch Cancer Society) and a prepaid return envelope. Patients who did not return the documents within two weeks received a reminder call.

After receiving the returned documents, patients were randomized between standard care (control group) or access to the ENCOURAGE program (intervention group) by a data-manager of the UMCG. The patients were allocated with a computer-generated randomization list using blocked randomization to conceal the allocation sequence until intervention assignment (allocation ratio 1:1; block size of 4; stratified per hospital). Patients were informed by phone by the research psychologist about the randomization outcome. Blinding of patients or the research team was not applied.

Patients received questionnaires at 6 (T1) and 12 weeks (T2) by mail. If questionnaires were not returned after 1 week, patients received a reminder e-mail. Patients were contacted by telephone if they did not respond within 1 week after the reminder.

Intervention and control condition

Key features of ENCOURAGE (http://lastmeter.medischeoncologiegroningen.nl; username: JPainSymptomManage; password: Symptom1; Appendix 1) were inspired on problem-solving therapy [17,18]: 1) *Problem **orientation and** identification:* an online version of the Dutch Distress Thermometer (DT) and accompanying 47-item Problem List (PL) covering practical, family/social, emotional, religious/spiritual and physical problems [25] was used to identify the problems patients experienced. After completion, patients immediately received online feedback about their distress score. The feedback identified three levels of distress severity (DT=0-4 for no or mild distress; DT=5-7 moderate distress and DT=8-10 severe distress [25]); 2) Subsequently, patients received fully automated *tailored psycho-education* for the reported problems. Psycho-educational material was written for **30** problems separately, from a re-entry specific viewpoint **(Appendix 2).** Psycho-education comprised background information about problems **(including normalization)**, possible problem-solving strategies for coping, resources including hyperlinks to other websites and services (for self-referral). Completed DT/PL's were automatically saved online to ensure access to the psycho-educational material any time later. **All** DT/PLs that were (partly) completed **by patients were registered for study purposes**. Program content was fixed during the 12 weeks. Patients could contact the research psychologist (telephone/e-mail) to discuss any questions and/or problems.

The content of the ENCOURAGE program was based on contemporary scientific literature and input from a multidisciplinary team of psychologists, oncology nurses, medical oncologists, a pastoral worker and a patient advocate. Breast cancer patients within 9 months after chemotherapy completion from the UMCG (N=12) evaluated the content of the program positively in terms of usefulness **(Cohen's *d*=0.30)**, feeling informed **(0.66)** and increased optimism and control over the future **(0.96)** in a small **single** arm pilot study **compared to patients >9 months after chemotherapy (N=7).**

Patients assigned to the intervention group, had access to the program during 12 subsequent weeks. An e-mail was sent to patients containing a leaflet that introduced the ENCOURAGE program together with log-in information. Patients were requested to visit the program **and to complete the online DT/PL** at least once during the first 7 days after **receiving login information to ensure that all participants received some amount of psycho-educational material**. The research psychologist contacted patients that had not accessed the program within the first week (a reminder mail was send, after 2 weeks they received a telephone call). No further use requests were imposed.

Standard care consisted of regular visits to a medical specialist (medical, surgical or radiation oncologist and/or oncology nurse) every 3 or 4 months during the first follow-up year. Patients were referred to additional health care by their oncologist and/or oncology nurse in case of unmet needs and/or a referral wish.

Measures

At baseline (T0), patient characteristics, health care use, distress and quality of life were assessed. **At 6 (T1) and 12 weeks (T2) optimism and control over the future, feeling informed and acceptance of the illness, were measured. At 12 weeks (T2) patients' health care use, distress and quality of life were re-assessed.** At T2, the intervention group also received a questionnaire regarding website opinion and use (T2).

A self-report questionnaire was used to assess socio-demographic characteristics. Illness-related characteristics and treatment received were collected from patients' medical records. The questionnaire also asked whether psychosocial and/or paramedical health care had been used before breast cancer diagnosis, after diagnosis and/or during study enrollment.

Increased optimism and control over the future' (primary outcome) is an 8-item subscale (Cronbach's alpha=0.75 (T1); alpha=0.79 (T2)) of the 'Constructs Empowering

Outcomes' (CEO) questionnaire [26]. **This questionnaire is developed and tested in various online support groups including breast cancer patients** [27,28]. The subscales 'feel better informed' (4 items; alpha=0.94; alpha=0.94) and 'improved acceptance of the illness' (5 items; alpha=0.92; alpha=0.94) were also measured. The questionnaire assesses retrospectively to what extent patients experience certain outcomes by their participation in an online support group. We changed 'online support group' into 'website' and 'information leaflets' for the intervention and control group, respectively. All items began with the statement: 'Through the use of the website/information leaflets…'. Patients could answer on a 5-point scale ranging from 'completely disagree' (1) to 'completely agree' (5). For each subscale a mean total score was calculated. Total scores were not calculated for the CEO questionnaire as the subscales measure heterogeneous constructs [27].

Distress was measured using the Dutch DT/PL [25,29]. The DT consists of a single item that asks patients to indicate the amount of distress experienced during the past week on an 11-point scale (0-10; no to extreme distress). On the 47-item PL, patients could indicate whether or not (yes/no) they experienced certain problems. Patients were asked to rate from 1-10 the amount of distress they experienced for each item in the PL they answered 'yes'. Lastly, the questionnaire measures patients' referral wish (yes, maybe or no) to a health care professional.

Quality of Life (QoL) was measured using the EORTC QLQ-C30, version 3.0 [30] and the QLQ-BR23 [31]. Global health status/QoL and the functional scales of these questionnaires (physical, role, cognitive, emotional, social functioning and body image, sexual functioning, sexual enjoyment and future perspective) were included.

The Technology Acceptance Model (TAM) questionnaire [32] was used to assess patients' opinion of the ENCOURAGE program. The subscales 'perceived usefulness' (3 items, alpha=0.94), 'positive attitude' (1 item) and 'actual usage' (1 item) were assessed.

Items are rated on a 5-point Likert scale, ranging from 'completely disagree' (1) to 'completely agree' (5). At the end of the questionnaire, patients had the opportunity to comment on the program in free text format.

Data analysis

The power analysis was performed on the difference for the mean subscale score of 'increased optimism and control over the future' between the control and intervention group at 12 weeks (T2). We aimed to recruit 128 patients (64 in each group) to detect a medium effect size of 0.50 using a two-tailed test (β=0.80; α=0.05 (G*power [34])). Recruitment continued until 128 patients returned the T2 questionnaire.

The range of missing values was 0.0%-13.8% for all variables except for distress at T2. This variable had 24.6% missing values. Missing data patterns were examined and subsequently multiple imputed (20 imputations) by use of the fully conditional specification algorithm [35,36]. The results of the complete case analyses were similar to the results of the imputed datasets (N=138). Therefore, we decided to report the results based on the analyses of the original data.

Descriptive statistics were calculated for socio-demographic and illness-related characteristics, CEO scales, TAM scales, QoL, the DT/PL and health care use. Analyses were performed according to the intention-to-treat principle. Separate ANCOVAs were performed to examine the effect of study group on the CEO scales and on changes in the DT/PL and QoL domains from baseline to T2. Differences between the study groups in patient characteristics, health care use and/or baseline measures were included as covariates in the ANCOVA models. Separate ANCOVA analyses were performed for clinically distressed

breast cancer patients. Patients were defined as clinically distressed with a baseline DT score ≥5 [25,37]. These subgroup analyses were unplanned and therefore, underpowered. If standardized residuals of the ANCOVA model were non-normally distributed, the outcome variable was dichotomized (stable/improved scores versus worsened scores) and analyzed by a logistic regression analysis. Effect sizes were calculated by Cohen's *d* for independent groups (mean unadjusted difference between the study groups divided by the pooled standard deviation). Statistical analyses were performed by SPSS (v23; SPSS Inc. Chicago, IL).

RESULTS

Patient characteristics

Of the approached 207 patients, 139 were enrolled in the study between January 2013 and October 2014. Figure 1 displays the CONSORT diagram. Patients not interested to participate most often reported that they were too busy or did not want to be confronted with cancer-related information. Characteristics of the patients in the control and the intervention group are provided in Table 1. Less patients in the control group received immunotherapy during the study period than patients in the intervention group (χ^2=4.0, *P*=.047). No differences between study completers and dropouts were observed for the baseline measures.

Use and evaluation of the ENCOURAGE program

According to the log files, two patients never visited the program. One of these patients returned the questionnaires and the intention-to-treat principle was applied. Eighteen patients did not log in within 1 week and were reminded by e-mail. Seven patients received an additional phone call as they had not logged in after 2 weeks. These contacts focused on program access and support was only provided for technical issues. The number of online DT/PLs patients started, ranged from 0-7 (median=2; N=69), with

61% of the patients logging in more than once. Self-reported use of the program was similar to this usage statistic (range 0-6; median=2; N=62).

The mean score patients assigned to the usefulness of the program was 3.55 (SD=0.89; N=59). Of the patients, 71% agreed (score=4) or completely agreed (score=5) with having a positive attitude towards the program. Ten percent was not satisfied with the program.

Three patients contacted the research psychologist to discuss problems and/or health care needs. The number of problems reported **on the online DT/PLs** ranged from 0 to 30 (M=14; SD=6). Psycho-education was **provided most often (89x) for** 'lack of physical fitness' (73% **of** total number **of** completed PLs)), 'fatigue' (71%), 'problems with appearance' (56%), 'tingling in hands/feet' (55%) and 'lack of muscle strength' (55%).

Primary and secondary outcomes

No significant difference was detected in 'increased optimism and control over the future' at T2 between the control and the intervention group. Also, no effects were detected for the primary outcome at T1. Patients in the control group reported higher scores for 'being better informed' and 'increased acceptance' than patients in the intervention group at T1. At T2, no differences between the study groups for these outcomes were obtained (Table 2). Both study groups improved equally well between T1 and T2 regarding 'increased optimism and control over the future', 'being better informed', and 'increased acceptance'. Improvements in distress, distress-related problems and QoL were observed in both study groups **but no significant differences were observed between the groups at T2** (Table 3).

Distressed breast cancer patients

Several patients reported that they did not felt supported by the ENCOURAGE program since they did not experience high distress for which they needed additional support. Therefore, we

decided to analyze the 57 (41%) clinically distressed patients separately (*N*=21 in the intervention group, *N*=26 patients in the control group, *N*=10 missing data at T2).

Usefulness of the program was rated with a 3.75 (SD=0.75; N=21). Seventeen of 21 distressed patients (81%) randomized in the intervention group agreed or completely agreed with having a positive attitude towards the program. More distressed patients in the intervention group **(15%)** than in the control group **(38%)** received **radiotherapy during the study period (χ^2=3.15, *p*=0.076, N=47)**.

The clinically distressed patients in the intervention group reported a higher increase in optimism and control over the future at T2 than the patients in the control group (Table 2). Additionally, in the intervention group (M_{change}=**0.25**), but not in the control group (M_{change}=**0.02**), 'increased optimism and control over the future' improved from T1 to T2 (**95% CI=0.06-0.58, *F*(1,40)=6.31, *P*=.016, Cohen's *d*=0.51**). No between-group effects were observed for the secondary outcomes (Table 3).

Discussion

This study was **among** the first that evaluated the effects of a web-based tailored psycho-educational intervention for breast cancer patients in the re-entry phase. Although results showed no harmful effects of the ENCOURAGE program, **no additional beneficial effects of the program compared to the information leaflets that are part of standard care**, were observed.

An explanation for the absence of effects may be that certain patients could not further increase in optimism and control over the future. For example, patients who suffer from minor symptoms may not experience an increase herein after use of the program as they feel that their symptoms are already in control. Thus, the program may be effective for a subgroup of patients only. This hypothesis may be reflected by our finding that the program increased

feelings of optimism and control over the future more than standard care in the subgroup of patients with clinically elevated distress at baseline. This might imply that distressed patients benefit from such a web-based program. About 30-60% of breast cancer patients suffer from clinically elevated distress during the first 6 months after treatment completion [38]. Similarly, we found 41% of the breast cancer patients to be distressed at baseline of the study. If the program is of help to distressed patients, a relatively large patient population may benefit from the use of the ENCOURAGE program. However, this is a premature conclusion and the results of the subgroup analyses should be interpreted with caution as they were unplanned and underpowered.

Methodological considerations

The absence of findings may, in part, be explained by the design of the program and the intervention onset. Considering the rather low program use, patients may have been exposed too little to the content of the program to solicit any **observable** effect. **The ENCOURAGE program adopted a problem-solving orientation. Problem solving therapy (PST) includes the elements: problem orientation, problem definition, generation of alternatives, decision-making, solution implementation and verification that should be stepwise addressed [18]. Our program incorporated problem orientation and problem definition but the other elements were only implicitly addressed in the psycho-educational material. About 10 sessions are recommended to deliver an effective PST intervention [18,19]. During the 12-week access to the program, patients were not guided throughout all the PST phases, probably contributing to the absence of effects. Future research with the ENCOURAGE program should incorporate all PST phases with homework assignments to practice new skills. The adapted program should be**

tested in distressed patients, immediately after completion of chemotherapy to ensure that survivors receive support at an early phase.

Positive adjustment questionnaires, like the CEO questionnaire, are scarce. This questionnaire suited the purposes of the current study: it was specially developed to assess outcomes by the use of web-based programs and was tested in breast cancer patients. However, as baseline scores could not be derived due to its retrospective nature and it is not extensively validated, it might lack sensitivity to measure change.

Several strengths can be noted. The current RCT evaluated a web-based psycho-educational program that targets a gap in survivorship care wherein breast cancer patients report high unmet needs [1,6]. **At present, very few of such programs are available.** The study was conducted in line with the CONSORT statement for reporting eHealth interventions [39,40]. The included patients **varied in socio-demographic and illness-related characteristics and distress reflecting the representativeness of the current sample.**

Conclusion

In contrast to our expectations, no effects in favor of the ENCOURAGE program were observed. Given the findings that especially distressed patients evaluated the program positively, a subgroup of breast cancer patients might benefit from this intervention. **We aim to further develop and test the program. The valuable information of the current study** can be used as a starting point for further improvement and use of the program.

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Conflict of interest

The authors declare that they have no conflict of interest.

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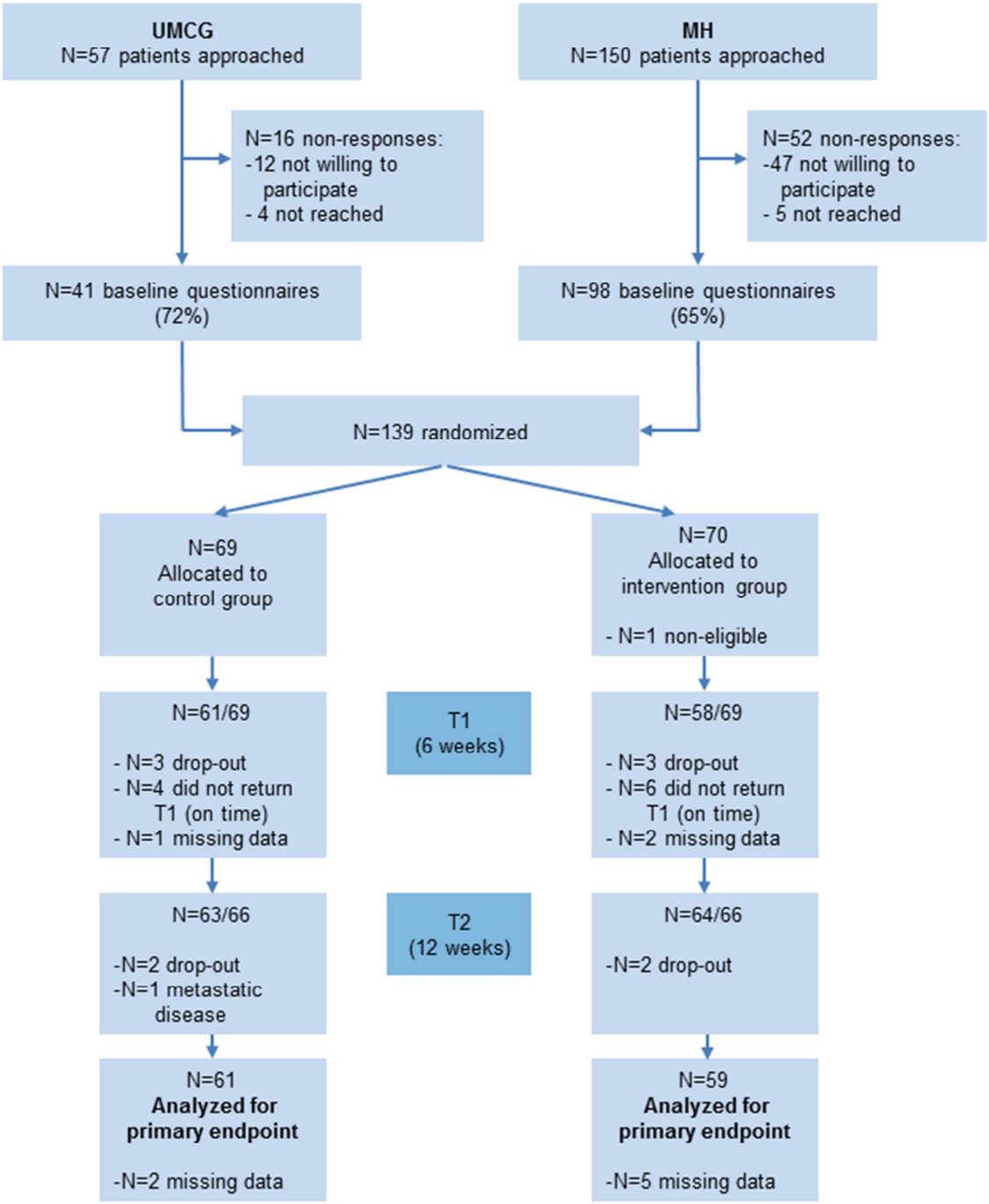

Figure 1.

CONSORT diagram of patient flow from patient approach to analyses.

UMCG: University Medical Center Groningen; MH: Martini Hospital

Table 1.
Patient characteristics at baseline (*N*=138).

	C		I		
	N	M±SD	N	M±SD	*P*
Age (years)	69	53.2±8.5	69	53.1±9.8	.920
Time since diagnosis (months)	69	8.7±1.9	69	8.7±2.1	.920
Time since chemotherapy (months)	69	2.4±1.7	69	1.9±1.5	.078
	C		I		
	N	%	N	%	*P*
Marital status					
Married/living together	50	73	54	78	.429
Single/widowed/divorced/LAT	19	28	15	22	
Children					
Yes	57	83	60	87	.477
No	12	17	9	13	
Children at home					
Yes	29	42	38	55	.125
No	40	58	31	45	
Educational level					
Lower vocational	4	6	5	7	.298
Secondary education/higher general	32	46	40	58	
Higher vocational/University	33	48	24	35	
Employment					
Yes	44	64	36	52	.168
No	25	36	33	48	
Cancer stage					
I	33	48	30	44	.561
II	1	1	3	4	

III	35	51	36	52	
Breast cancer type					
IDC	54	78	58	84	.477
ILC	10	15	9	13	
Other	5	7	2	3	
Surgery					
Lumpectomy	35	51	33	48	.733
Mastectomy	34	49	36	52	
Cancer treatment during study					
Cosmetic surgery[a]					
Yes	7	10	5	7	.546
No	62	90	64	93	
Radiotherapy[a]					
Yes	11	16	20	29	.066
No	58	84	49	71	
Immunotherapy[a]					
Yes	8	12	17	25	**.047**
No	61	88	52	75	
Hormone therapy					
Yes	51	74	50	73	.848
No	18	26	19	28	
Health care use					
Before diagnosis					
Yes	**26**	**38**	**30**	**43**	**.488**
No	**43**	**62**	**39**	**57**	
After diagnosis					
Yes	**42**	**61**	**44**	**64**	**.725**
No	**27**	**39**	**25**	**36**	
During study					**.145**
Yes	**42**	**67**	**34**	**54**	

No	**21**	**33**	**29**	**46**

M=mean; SD=standard deviation; I=intervention group; C=control group; ns=non-significant
Indepent-samples t-tests (continuous variables) and X^2 tests (categorical variables) were used to examine differences between study groups.

Table 2.
Group means and differences for empowering outcomes for the control and intervention group.

	At 6 weeks (T1)							At 12 weeks (T2)						
	C		I		Group differences			C		I		Group differences		
CEO subscale	M±SD	N	M±SD	N	I – C (95% CI)[ab]	*P*[ab]	ES	M±SD	N	M±SD	N	I – C (95% CI)[ab]	*P*[ab]	ES
Complete sample														
Increased optimism and control	3.09±0.54	61	3.14±0.50	58	0.06 (-0.13, 0.26)	.515	0.11	3.10±0.57	61	3.18±0.52	59	0.10 (-0.10, 0.30)	.312	0.15
Being better informed	3.73±0.57	60	3.39±0.82	58	-0.31 (-0.57, -0.05)	.020	0.48	3.56±0.65	62	3.31±0.86	60	-0.24 (-0.52, 0.04)	.088	0.33
Improved acceptance	3.09±0.88	61	2.78±0.79	58	-0.32 (-0.63, -0.01)	.044	0.37	3.04±0.90	62	2.73±0.88	60	-0.26 (-0.58, 0.06)	.114	0.35
Distressed patients														
Increased optimism and control	3.03±0.59	26	3.10±0.61	22	**0.08 (-0.28, 0.44)**	**.666**	0.11	2.97±0.57	26	3.34±0.59	21	**0.43 (0.85, 0.78)**	**.017**	0.65
Being better informed	3.69±0.65	25	3.44±0.90	22	**-0.27 (-0.74, 0.20)**	**.246**	0.31	3.49±0.69	27	3.38±0.86	22	**-0.13 (-0.62, 0.35)**	**.584**	0.15
Improved acceptance	3.13±0.97	26	2.85±0.80	22	**-0.32(-0.85, 0.22)**	**.236**	0.32	2.96±0.93	27	3.08±0.77	22	**0.08 (-0.43, 0.59)**	**.751**	0.14

M=mean; SD=standard deviation; C=control group; I=intervention group; ES=effect size
[a]Complete sample=adjusted for the variable 'receiving current immunotherapy'; [b]Distressed patients=adjusted for the variable **'receiving current radiotherapy'**

Table 3.
Group means and differences for distress, distress-related problems and QoL for the control and intervention group.

	Baseline (T0)				Δ12 weeks (T2)				
	C		I		C	I	Group differences		
Outcome	M±SD	N	M±SD	N	M±SD	M±SD	Δ I - C (95% CI) [ab]	*P* [ab]	*ES*
Complete sample									
Distress									
DT	4.65±2.00	51	3.82±2.24	49	-0.59±2.55	-0.20±2.15	-0.02 (-0.91, 0.87)	.964	0.16
Problem domains									
Practical	0.74 ±0.96	63	0.81±1.05	61	-0.16±1.03	-0.25±1.16	0.96 (0.39, 2.38)[c]	.936	
Social	0.30±0.99	62	0.51±1.09	62	0.04±1.22	-0.27±0.84	5.08 (0.49, 52.58)[c]	.173	
Emotional	1.38±1.30	58	1.48±1.72	58	-0.08±1.32	-0.34±1.41	-0.27 (-0.68, 0.14)	.190	0.19
Spiritual	0.52±1.31	61	0.54±1.48	61	-0.24±1.19	-0.37±1.11	0.76 (0.11, 5.39)[c]	.787	
Physical	1.53±1.18	60	1.45±1.15	57	-0.64±1.02	-0.58±1.01	-0.06 (-0.28, 0.16)	.588	0.06
QoL – EORTC-C30									
Global health status/QoL	67.46±18.74	63	68.55±17.56	62	5.95±17.67	5.78 ±19.42	0.90 (-4.33, 6.12)	.735	0.01
Functional scales									
Physical	76.83±16.76	63	79.68±17.64	62	9.21±13.52	6.42±15.33	-0.61 (-4.42, 3.21)	.754	0.19
Role	63.23±27.62	63	66.94±29.18	62	11.11±25.92	9.68±25.53	2.44 (-4.70, 9.57)	.500	0.06
Emotional	82.01±17.91	63	80.03±19.83	63	1.41±17.26	2.29±19.06	0.08 (-5.22, 5.39)	.976	0.05

Cognitive	75.93±18.64	63	79.37±21.53	63	5.03±14.86	3.97±20.02	2.28 (-2.77, 7.33)	.374	0.06
Social	76.19±27.55	63	77.96±22.34	62	8.47±25.38	11.02±20.46	4.24 (-1.63, 10.10)	.155	0.11
QoL – BR23									
Body image	77.42±22.55	62	69.53±25.77	64	5.11±15.63	11.46±23.03	2.91 (-3.05, 8.78)	.335	0.32
Sexual functioning	20.43±21.00	62	14.41±18.94	59	6.45±15.78	8.47±15.59	0.52 (-4.93, 5.98)	.850	0.13
Sexual Enjoyment	60.26±24.98	26	45.00±31.11	20	5.13±22.49	10.00±21.90	-0.46 (-12.47, 11.56)	.940	0.22
Future perspective	66.67±25.61	62	60.42±25.11	64	0.54±22.17	5.73±25.58	3.94 (-3.69, 11.57)	.309	0.22
Distressed subgroup									
Distress									
DT	6.46±1.22	24	6.50±1.37	16	-1.67±2.53	-1.19±1.42	**0.14 (-1.24, 1.53)**	**.835**	0.23
Problem domains									
Practical	1.14±1.18	28	1.51±1.23	23	-0.35±1.27	-0.66±1.36	**0.93 (0.22, 3.94)[c]**	**.916**	
Social	0.83±1.33	27	0.97±1.52	23	-0.02±1.83	-0.61±0.99	**2.76 (0.15, 47.20)[c]**	**.503**	
Emotional	1.99±1.43	24	2.80±1.94	22	-0.57±1.51	-1.20±1.78	**-0.36 (-1.16, 0.45)**	**.374**	0.38
Spiritual	1.06±1.82	27	1.27±2.21	22	-0.67±1.52	-0.86±1.59	**1.08 (0.08, 14.24)[c]**	**.952**	
Physical	2.06±1.18	27	2.21±1.16	22	-1.03±1.01	-1.09±1.26	**0.21 (-0.40, 0.44)**	**.919**	0.05
QoL – EORTC-C30									
Global health status/QoL	59.52±19.74	28	58.70±15.78	23	10.42±21.35	10.51±19.50	**0.43 (-8.91, 9.76)**	**.927**	0.00

Functional scales									
Physical	69.29±17.90	28	67.25±18.08	23	13.57±15.45	12.46±15.35	**-2.05 (-9.09, 4.99)**	**.561**	0.07
Role	54.17±29.62	28	47.83±30.69	23	17.26±26.25	17.39±23.83	**-3.38 (-15.45, 8.68)**	**.575**	0.00
Emotional	72.32±19.78	28	67.39±24.22	23	5.56±19.47	10.14±24.87	**4.38 (-5.31, 14.06)**	**.368**	0.21
Cognitive	73.81±18.94	28	70.29±25.60	23	8.33±14.70	12.32±22.60	**3.28 (-5.88, 12.43)**	**.475**	0.21
Social	62.50±32.27	28	63.04±21.29	23	17.26±32.55	21.74±20.98	**5.03 (-7.20, 17.26)**	**.412**	0.16
QoL – BR23									
Body image	71.91±24.04	27	57.61±26.34	23	6.48±17.19	19.93±27.61	**6.65 (-5.22, 18.51)**	**.265**	0.58
Sexual functioning	17.28±21.92	27	18.18±21.15	22	9.26±18.68	9.09±16.04	**0.64 (-9.23, 10.51)**	**.897**	0.00
Sexual Enjoyment	62.50±27.82	8	43.33±31.62	10	8.33±29.55	16.67±23.57	**-0.75 (-24.85, 23.34)**	**.948**	0.31
Future perspective	58.02±25.47	27	46.38±31.36	23	2.47±22.51	15.94±26.34	**11.10 (-2.31, 24.50)**	**.103**	0.55

M=mean; SD=standard deviation; C=control group; I=intervention group; ES=effect size
[a]Complete sample=adjusted for the variable 'receiving current immunotherapy'; [b]Distressed patients=adjusted for the variable **'receiving current radiotherapy'**
[c]Logistic regression: Exp(B) and 95% CI for Exp(B) are displayed